REMARKS

Prior to entry of the foregoing amendment, claims 1-18, 49, 51-55, 58-60, 62, 63 and 68-71 were pending. By the foregoing amendment, claims 1, 49, 53, 63, 68 and 71 have been amended; claims 5, 52, 58-60 and 62 have been canceled; and, new claims 72-76 have been added. Therefore, upon entry of the foregoing amendment, claims 1-4, 49, 51, 53-55, 63 and 68-76 will be pending. Of these, claims 1, 49 and 72 are independent claims. Entry of the foregoing amendments and reconsideration of the subject application are respectfully requested.

As discussed more fully below, claim 1 has been amended to recite that R^3 is phenyl; claim 49 has been amended, to obviate the Examiner's section 112, 2nd paragraph rejection of claims 68-71 (which are dependent either directly or indirectly from claim 49), to recite that R^2 is methyl and R^3 is phenyl; claim 53 has been amended to render it consistent with the amendment to claim 1, from which it depends; claim 63 has been amended to render it consistent with the amendment to claim 49, from which it depends; and, claims 68 and 71 have been amended in response to the Examiner's section 112, 2nd paragraph rejection. New independent claim 72 has been added to cover compounds that were only excluded from the scope of claim 49 to obviate the section 112, 2nd paragraph rejection of claims 68-71, dependent from claim 49. New dependent claims 73-76, further define the compounds of claim 72 and substantially correspond, respectively, to claims 59, 60, 62 and 63, which were canceled in view of the amendment to claim 49.

The Examiner has indicated that dependent claims 54, 55 and 63 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. This indication of allowable subject matter is thankfully acknowledged.

Applicant also submits herewith a copy of PTO Form 1449, which was inadvertently omitted from the Information Disclosure Statement filed June 9, 2003.

I. Rejection Under 35 U.S.C. § 112, 1st paragraph

Claims 1-18, 49, 51-53, 58-60 and 62 have been rejected under 35 U.S.C. §112, 1st paragraph, as allegedly not being supported by an enabling disclosure. This rejection is traversed

insofar as the Examiner considers it applicable to any claim pending in the subject application upon entry of the foregoing amendment and consideration of the remarks below.

It is respectfully submitted that this rejection is obviated with respect to claims 52, 58-60 and 62, which have been canceled by the foregoing amendment. Claim 49 has been amended such that R^1 is tosyl, formyl or benzoyl; R^2 is alkyl; and, R^3 is phenyl. The compounds of claim 49 are the same compounds covered by claim 54, which the Examiner indicated allowable. It is respectfully submitted that claim 49 is, therefore, also allowable.

The Examiner stated:

> The how to use rejection of previous actions still remains to a large degree. As stated in the action mailed 4/17/02, the instant process and reactants, and products made are disclosed to be solely useful in ultimately making mirtazapine or its derivatives as disclosed in U.S. 4,062,848 which is incorporated by reference on p.2 of the specification. In reviewing the scope of R variables permitted in the instant process and compound claims it is noted the scope entails far more than what is ultimately taught to be within the disclosure of US'848. Compare instant R2 scope with R2 in van der Burg as well as scope of R3 with R1-containing phenyl ring in US'848. Also it is not seen how R3 other than phenyl can make the outer phenyl ring present in mirtazapine. Additionally cleavage of **all** R1 variables has not been shown can be achieved employing the hydrolysis condition shown for R1 as tosyl. Note R1 can still be phenylalkoxy in process claims.

The Examiner is respectfully requested to note that the R^3 substituent in independent claims 1 and 49, as well as in new independent claim 73, is recited to be phenyl. When R^3 is phenyl, the compounds are useful in making mirtazapine and its derivatives, in which the phenyl ring corresponding to the R^3 substituent corresponds, as the Examiner refers to it, the "outer phenyl ring" present in the tetracyclic structure of mirtazapine and its derivatives. It is respectfully submitted that the Examiner's objections to the scope of the R^3 substituent are, therefore, obviated by this amendment.

The Examiner appears to desire Applicant to limit the scope of the R^2 group to be the same as defined in the '848 patent (which discloses mirtazapine and its derivatives), i.e., "hydrogen, lower alkyl or aralkyl." It is true that, in the subject application, the R^2 substituent is

defined to include alkoxy, phenyl, phenyloxy and phenyalkoxy, which are R^2 substituents not expressly disclosed in the '848 patent, which has been incorporated into the subject specification by reference.

In order to properly reject claims under section 112, 1st paragraph for allegedly failing to provide an adequate disclosure enabling one skilled in the art how to make and use the claimed invention without undue experimentation, it is encumbent upon the Examiner to provide a reasonable basis to doubt the objective truth of the statements made in the specification regarding enablement. *See, e.g., In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993) and *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971). According to *In re Bowen*, 492 F.2d 859, 862-63 (CCPA 1974), the examiner must provide sufficient reasoning for doubting the enablement of the claims, even when there is no evidence in the record of operability without undue experimentation beyond the disclosed embodiments. *See also*, MPEP section 2164.04.

Applicants have disclosed that the compounds having an R^2 substituent as presently defined in claims 1, 49 and 72 are useful, *inter alia*, in making compounds useful as intermediates in the synthesis of mirtazapine and structurally related piperazinoazepine compounds. Piperazinoazepine compounds such as mirtazapine are useful as antidepressants. It is respectfully submitted that the mere fact that Applicants have incorporated the '848 patent by reference into the subject specification and that the '848 patent has an arguably more limited definition for the corresponding R^2 substituent, does not provide an objective basis upon which the Examiner's section 112, 1st paragraph rejection can be properly maintained. Other than citing the more limited scope of the '848 patent in respect to the corresponding R^2 substituent, the Examiner has provided no explanation as to why the scope of the R^2 substituent in the present claims is not adequately enabled. In the absence of such evidence, it is respectfully submitted that this aspect of the enablement rejection is improper and withdrawal thereof is respectfully requested.

The foregoing comments are also applicable to the Examiner's objection to the scope of the R^1 substituent, which is recited in independent claims 1 and 72 to be phenylalkoxy, tosyl, benzoyl or formyl and in claim 49 to be tosyl, benzoyl or formyl. Based on the indication that

claim 54 is allowable, the Examiner does not appear to have any objection to R^1 being tosyl, benzoyl or formyl, as the R^1 substituent in claim 54 is so limited. The Examiner, however, appears to doubt, without providing any objective basis therefore, whether phenylalkoxy, as an R^1 substituent, can be hydrolyzed using an acid as disclosed in the subject specification. It is respectfully submitted that one skilled in art would understand that phenylalkoxy can be removed from a piperazinyl ring nitrogen using acid hydrolysis, particularly using a strong acid such as disclosed in the specification at page 5. One skilled in the art would certainly not have to engage in undue experimentation to remove a phenylalkoxy substituent by acid hydrolysis. Therefore, it is respectfully submitted that the definition of R^2 as phenylalkoxy, tosyl, benzoyl or formyl is fully enabled by the subject specification. Reconsideration and withdrawal of this aspect of the section 112, 1st paragraph rejection is respectfully requested.

II. Rejections Under 35 U.S.C. § 112, 2nd Paragraph

Claims 68-71 have been rejected under 35 U.S.C. §112, 2nd paragraph, as allegedly being indefinite.

The Examiner notes that the term "the acid" in claim 69 lacks antecedent basis in claim 68, from which claim 69 depends. Claim 68 has been amended to recite that the hydrolysis is conducted in an acid. This amendment is supported by the specification at page 5, lines 14-19. Withdrawal of this aspect of the section 112, 2nd paragraph rejection is respectfully requested in view of this amendment.

The Examiner has requested that "piperazynyl" in claim 71 be changed to –piperazinyl--. The spelling corrections have been made. Accordingly, withdrawal of this aspect of the section 112, 2nd paragraph rejection is respectfully requested.

Finally, the Examiner states that throughout the claims, "the compound of claim 49 is recited but never identified. Given the preparation of one species in these claims only one compound in claim 49 is being employed and the claims should clearly reflect this."

Claim 49 has been amended to define the R^2 substituent as methyl, and the R^3 substituent as phenyl. Each of claims 68, 70 and 71 recites preparing the compound 4-methyl-2-phenylpiperazine by "hydrolyzing the compound of claim 49." Acid hydrolysis of the compound of claim 49, where the R^2 substituent is methyl, and the R^3 substituent is phenyl, will result in 4-methyl-2-phenylpiperazine. It is not necessary to limit the R^1 group to a single substituent, because R^1 represents a hydrolyzable group that is removed by the step of hydrolysis. Therefore, R^1 is variable and any of the compounds of formula IV in claim 49, where R^1 is tosyl, formyl or benzoyl; R^2 is methyl; and, R^3 is phenyl can be used to make 4-methyl-2-phenylpiperazine as recited in claims 68-71. Accordingly, it is respectfully submitted that this aspect of the section 112, 2nd paragraph rejection be withdrawn.

CONCLUSION

Entry of the foregoing amendments is respectfully requested. In view of the foregoing amendments and remarks, an early and favorable action on the merits is earnestly solicited. The Examiner is invited to contact the undersigned attorney if such communication is believed to be helpful in advancing the examination of the present application. The Office is hereby authorized to charge any additional fees or credit any overpayments under 37 C.F.R. §1.16 or §1.17 to Deposit Account No. 11-0600.

Respectfully submitted,

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